FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

NDA 22465/S-010
Pazopanib (VOTRIENT®)
GlaxoSmithKline

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the VOTRIENT sNDA for the proposed indication of treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Proposed Indication

The applicant is seeking regular approval for the following indication.

> VOTRIENT is indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy.
>
> Important Limitations of Use: The Phase III STS trial population excluded patients with adipocytic STS or Gastrointestinal stromal tumors

2 Executive Summary

The applicant has submitted data from a single randomized, double-blind, phase 3 trial and one supporting single-arm phase 2 trial. In the phase 3 trial, patients with metastatic STS were randomized to pazopanib or placebo in a 2 to 1 manner. These patients were examined every 4 weeks for 12 weeks and then every 8 weeks until evidence of progression, death, excessive toxicity or patient withdrawal. Scans were read by an independent radiology review committee. The primary endpoint of this study was progression-free survival (PFS) although the study was also powered to evaluate overall survival (OS). Based on the results of the final PFS analysis, the median PFS was 4.6 months in the pazopanib arm and 1.6 months in the placebo arm. The hazard ratio was 0.35 [95% CI: 0.26, 0.48; $p < 0.001$.] Similarly, there was an improvement in the median PFS of 3 pre-specified histological subgroups of leiomyosarcoma, synovial sarcoma and "other" STS. However, this improvement in PFS did not translate into a statistically significant improvement in OS at the final analysis. The median OS was 12.6 months in the pazopanib arm and 10.7 months in the placebo arm with an HR of 0.87 [95% CI: 0.67, 1.12; p=0.26].

Pazopanib was previously approved for the treatment of patients with advanced renal cell carcinoma (RCC) in October 2009. The safety profile of pazopanib in patients with STS is generally similar to its safety profile in patients with RCC, with some differences that should be considered in conjunction with the efficacy findings. Generally, a higher proportion of patients on the pazopanib arm experienced a CTCAE Grade 3-4 AE (63% vs. 26%), an SAE (41% vs. 24%) or an AE leading to discontinuation of study therapy (20% vs. 5%) when compared to the placebo arm. The most clinically relevant AEs noted with more frequency in the pazopanib arm of the study included hepatotoxicity, myocardial dysfunction, hypertension, thromboembolic events, hemorrhagic events, pneumothorax and hypothyroidism.

3 Background

VOTRIENT (pazopanib) is a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet derived growth factor receptor (PDGFR)-α and-β, and c-kit tyrosine kinases. Pazopanib was previously approved for the treatment of patients with advanced renal cell carcinoma (RCC) in October 2009. Based on communications from the applicant, the decision to pursue an indication in STS was based on preclinical data suggesting high expression of VEGF in addition to other mediators of angiogenesis such as PDGF in STS. Additionally, in the phase 2 study performed in soft tissue sarcomas, an over all Progression Free rate (CR+PR+SD) at Week 12 of 41% (90% CI: 34.2%, 48.7%) was noted. Based on data from the EORTC Soft Tissue and Bone Sarcoma Group a Progression Free rate at 3 months of ≥40% is suggestive of activity in the setting of previously treated STS.

3.1 Treatment of Sarcoma

STS are a heterogeneous group of solid tumors that arise from a common mesenchymal precursor that differentiates into many different tissue lineages. Despite their common mesenchymal origin, each subtype of STS has distinctive clinical and pathological features. These tumors are pathologically classified based on the normal tissue they most closely resemble and more than 50 distinct histological subtypes of STS have been described, each with unique biological characteristics. These tumors can be further sub-classified depending on the pathological grade and anatomic location of the primary tumor at presentation. This heterogeneity of STS in addition to the rarity of these tumors has historically hampered drug development for this indication and the role of chemotherapy in the treatment of non-metastatic STS other than pediatric rhabdomyosarcoma remains controversial. It is however accepted that in patients with metastatic STS, judicious use of systemic therapy may provide symptom palliation, improve quality of life and delay progression and in some patients potentially prolong survival. This putative improvement in survival however has not been definitively demonstrated in controlled clinical trials and its magnitude, if any, is not defined.

Historically, anthracycline based chemotherapy regimens have been the treatment of choice in patients with STS. Specifically, doxorubicin, alone or in combination with ifosfamide, currently remains the standard of care for most patients. It is however becoming increasingly clear that different subtypes of STS have unique response patterns to chemotherapy and most experts now advocate the development of histology based therapeutic approaches. Table 1 summarizes agents currently used in the treatment of STS in the United States.

Table 1 Chemotherapy agents used for treatment of STS in the US*

Product	Approved for treatment of STS	Evidence of activity in STS
Doxorubicin	Yes	• Activity against multiple histologies of STS first described in 1970s. • Response rates in the range of 10-25% have been reported. • Approval for STS indication predates modern labeling. • When administered as part of combination regimens, response rates of up to 46% are seen although with inferior toxicity profile. • Unclear if liposomal doxorubicin has similar activity against STS although toxicity profile is better.
Ifosfamide	No	• Response rates of ≥ 25% have been reported in multiple trials. • Typically administered in combination with doxorubicin. • Active in multiple histologies particularly synovial sarcoma.
Dacarbazine	No	• Response rates of ≤18% have been reported in multiple histologies of STS.
Gemcitabine	No	• Higher response rates have been reported when administered in combination regimens. • In a randomized phase 2 study comparing gemcitabine with gemcitabine and docetaxel, response rate (16% vs. 9%), PFS (6.2 vs. 3.0 months) and OS (17.9 vs. 11.5 months) were all superior in the combination arm.
Paclitaxel	No	• Response rates of > 50% have been reported in patients with angiosarcoma.
Imatinib	Yes	• Approval based on objective response rate of 83% in 18 patients with dermatofibrosarcoma protuberans (DFSP)**.

* This table excludes therapies approved for treatment of GIST and rhabdomyosarcoma
** DFSP patients were excluded from the randomized phase 3 trial of pazopanib in STS

3.2 Regulatory History

An End of Phase 2 (EOP2) meeting was held with the applicant on December 18, 2007, to discuss the development of pazopanib for the STS indication. At this meeting the

applicant presented the preliminary results of the phase 2 study (VEG20002) in addition to their plans for the pivotal phase 3 study (VEG110727). The FDA made the following recommendations to the applicant:

1. Patients should have received previous therapy with all standard therapies including doxorubicin and ifosfamide.

2. Enrollment should be restricted to patients with metastatic disease.

3. FDA recommended that the study be powered for OS. The FDA specifically stated that in order "to consider PFS as a potential endpoint to support approval, the study should be powered for overall survival and you should incorporate an independent blinded radiologic review committee into the protocol for assessment of PFS. Furthermore, the magnitude of the effect should be robust and there should be an appropriate risk benefit ratio. Moreover, an increase in median PFS from 2.2 months to 3.5 months in this setting has uncertain clinical meaningfulness."

4. FDA recommended that the primary analysis be based on the ITT population.

4 Study Design

4.1 Studies Submitted to Support the Pazopanib STS sNDA

1. **VEG110727**: PAzopanib ExpLorEd in SofT-Tissue Sarcoma – A phasE III study (PALETTE)-"A randomized double blind phase III trial of Pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or following prior therapy."

2. **VEG20002**: Phase II study of GW786034 in patients with relapsed or refractory soft tissue sarcoma

4.2 VEG110727: Phase 3 Study Design

VEG110727 was a randomized, double-blind study of pazopanib vs. placebo (2:1 randomization) in patients with metastatic STS. The study was open to enrollment between October 2008 and February 2010. The schema of this study is summarized in Figure 1.

Key Eligibility Criteria (Summarized)

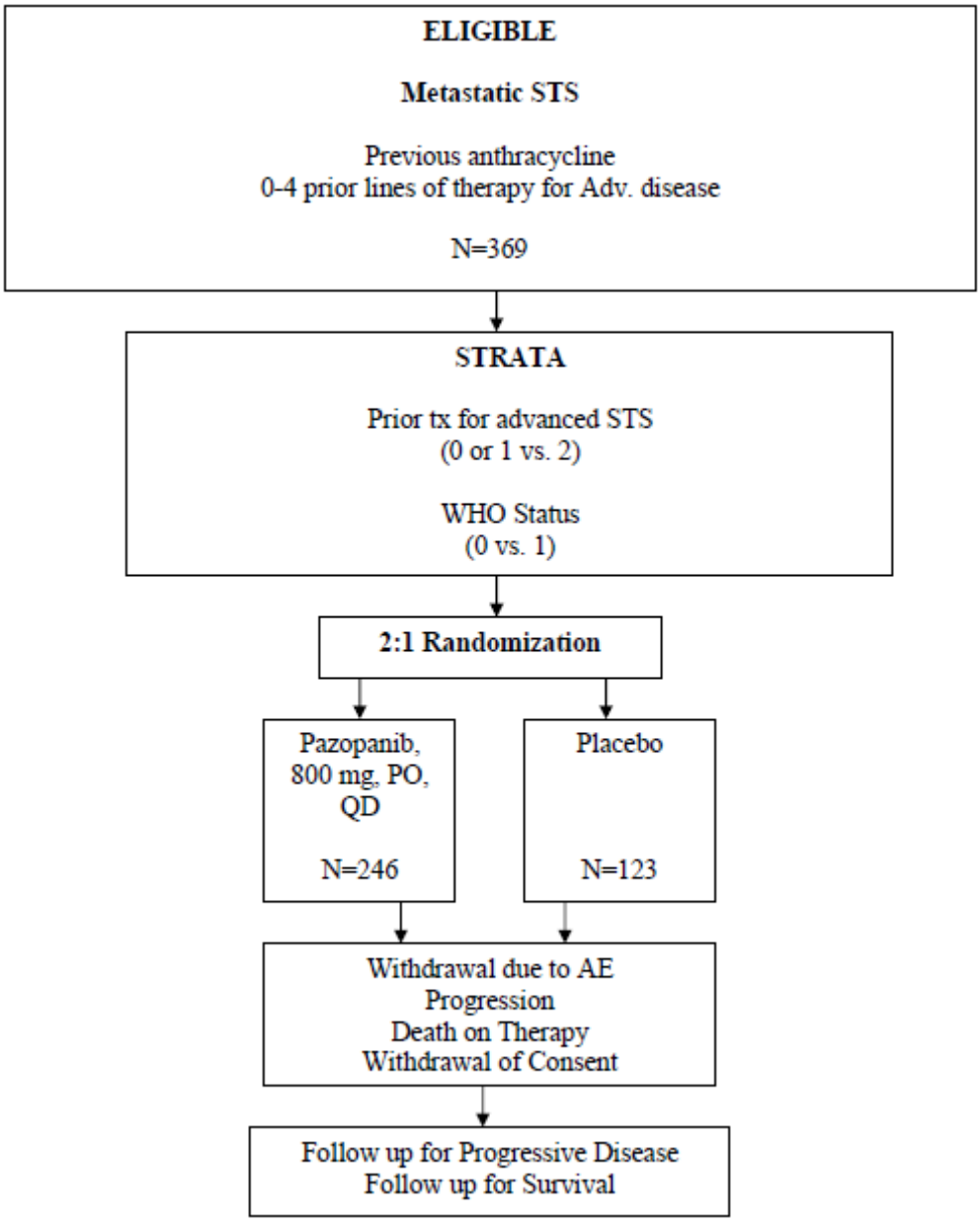
1. Histological evidence of high or intermediate grade malignant soft tissue sarcoma, or cytological evidence in case of presence of multiple metastases. Low grade tumors are allowed provided there is disease progression.

2. Presence of metastatic disease and not only locally advanced disease.

3. The following tumor types are eligible (WHO classification, 2008)
    a. Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumors)
    b. So-called fibrohistiocytic (pleomorphic “MFH”, giant cell “MFH”, inflammatory “MFH”)
    c. Leiomyosarcoma
    d. Malignant glomus tumors
    e. Skeletal muscles (pleomorphic and alveolar rhabdomyosarcoma)
    f. Vascular (epithelioid haemangioendothelioma, angiosarcoma)
    g. Uncertain differentiation (synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, PEComa, intimal sarcoma) excluding chondrosarcoma, Ewing tumors / PNET
    h. Malignant peripheral nerve sheath tumors
    i. Undifferentiated soft tissue sarcomas not otherwise specified
    j. Other types of sarcoma (not listed as ineligible), if approved by the medical monitors (written or e-mail approval needed prior to registration).

4. The following tumor types are ineligible
    a. Adipocytic sarcoma (all subtypes)
    b. Embryonal rhabdomyosarcoma
    c. Chondrosarcoma
    d. Osteosarcoma
    e. Ewing tumors / PNET
    f. Gastro-intestinal stromal tumors
    g. Dermofibromatosis sarcoma protuberans
    h. Inflammatory myofibroblastic sarcoma
    i. Malignant mesothelioma
    j. Mixed mesodermal tumors of the uterus

Figure 1 Study VEG110727 Schema



5. Formalin fixed paraffin embedded tumor blocks and representative H/E (hematoxylin/eosin) slides must be available for histological central review. Histological central review is not required before treatment start but it is mandatory to send the tumor blocks/slides to reference pathologists. Local histopathological diagnosis will be accepted for entry into the study.

6. The patients may have received a maximum of 4 prior lines of systemic therapies (including up to 2 combinations regimen) for advanced disease; (neo) adjuvant/maintenance treatments are not counted for this criterion.
    a. patients whose disease has progressed on or after anthracycline based regimen
    b. patients may not have been previously treated with inhibitors of angiogenesis and/or VEGF or VEGFR-targeting agents. mTOR inhibitors are not considered as inhibitors of angiogenesis.

7. At least 18 years of age

8. WHO performance status 0 or 1

9. Clinically normal cardiac function based on the institutional lower limit of normal (LVEF assessed by MUGA or ECHO),

10. Patients with poorly controlled (at baseline BP >150/90 is defined as poorly controlled) hypertension were ineligible.

Stratification Factors

1. Number of previous lines of therapy for advanced disease
    - 0 or 1
    - ≥ 2
2. Baseline WHO Performance Score
    - 0
    - 1

Treatment

1. Pazopanib 800 mg PO, QD
2. Placebo

Monitoring

- Performance status, vital signs and routine laboratories: CBC and chemistries were collected at screening, day 1, day 8 then q 4 weeks to week 12, then q 8 weeks until discontinuation, and at 4 week follow up
- LVEF was mandatory at baseline (within 14 days prior to the first dose of study drug), at Week 12 and every second scheduled visit thereafter until study drug discontinuation and end of therapy (or as clinically indicated).
- Disease assessment was performed at baseline and then every 4 weeks for 12 weeks, then every 8 weeks. Subjects were followed every 3 months for survival

data and data regarding follow up anti-cancer therapy after withdrawal of study therapy.

4.2.1 Independent Reviews

Data Monitoring Committee (DMC): An independent data monitoring committee met once to monitor the safety of subjects, and in particular the safety of subjects who had experienced cardiac dysfunction while on the study, and overall mortality, 23 months after the first subject was randomized. The OS data was reviewed by the DMC; however the study could not to be stopped due to benefit with respect to OS, but could have been stopped for harm. Therefore, other than for the planned, protocol-specified interim analysis for OS, there was no adjustment to the final significance level for OS.

Independent Review Committee (IRC): An IRC consisting of 2 reviewers reviewed all scans. Each set of scans for a subject were read by one radiologist (single-read) as a primary reviewer, and a subset of images were read by 2 radiologists to assess concordance (10 cases read by both reviewers). RECIST v 1.0 was used.

Central Pathology Review: Histological central review was not required before treatment start but it was mandatory to send tumor blocks/slides to one of two reference pathologists. Local histopathological diagnosis was accepted for entry into the study. Per the Reporting and Analysis Plan (RAP), diagnosis by central pathology review was used for all efficacy analysis except in cases were central review was not performed. In those cases local histopathological diagnosis was accepted.

4.2.2 Statistical Analysis Plan

The Reporting and Analysis Plan (RAP) for the phase 3 trial specified that the primary endpoint of the study is PFS “defined as the interval between the date of randomization and the earliest date of either disease progression or death due to any cause. For the primary analysis, progression is evaluated by the independent radiologist.” Additionally, the RAP specified that patients were to be censored, using the previous adequate assessment if the patient had not progressed prior to the clinical cut-off, if another anti-cancer therapy was initiated prior to progression, or if the patient’s progression event (PD or death) occurred after an extended period of inadequate assessment (PFS event occurred more than 8 weeks for visits occurring on or prior to the Week 12 visit and 12 weeks for visits occurring post the Week 12 visit). Patients without an adequate baseline assessment who did not die within 56 days from randomization were censored at randomization. The primary analysis was to be conducted in the intent to treat population using a stratified (WHO performance status, prior lines of treatment for advanced disease) log rank test with a two-sided alpha of 0.05. There was no planned interim analysis of PFS. The number of PFS events targeted in the final PFS analysis was 274.

The principle secondary endpoint specified in the RAP was overall survival (OS), defined as the interval between the date of randomization and the date of subject's death, whatever the cause. OS was to be analyzed in the ITT population. An interim analysis of OS was planned at the same time as the progression-free survival analysis with a Lan and DeMets alpha-spending function with an O'Brien and Fleming boundary with an overall alpha for OS of 0.05 (two-sided) to control the type 1 error rate. The final analysis of OS was planned at the time 279 deaths were observed. OS results were to be summarized using Kaplan-Meier survival curves, and compared between the treatment arms using a stratified log rank test (WHO performance status, prior lines of treatment for advanced disease).

Other key secondary endpoints included:

- PFS in 3 STS histological subgroups:
  - Leiomyosarcoma
  - Synovial Sarcoma
  - "Other" STS

- Overall response rate (ORR) defined as the percentage of subjects who achieved either confirmed CR or partial response (PR)

- Safety and tolerability including evaluation of Adverse Events (graded according to CTCAE, version 3.0) and changes from baseline in vital signs, laboratory parameters and LVEF.

5 Study Results

5.1 Patient Population

Baseline Demographics and Disease Characteristics

The baseline characteristics of patients on the phase 3 study VEG110727 were well balanced for age, sex, disease burden and performance status as is demonstrated in Table 2.

Table 2 Baseline Characteristics of patients on the Phase 3 Trial

Baseline Characteristics (ITT Population)		Placebo (N=123)	Pazopanib (N=246)
Age (yrs)		51 (18, 78)*	56 (20, 83)*
Sex	F	69 (56%)	147 (60%)
	M	54 (44%)	99 (40%)
# of sites of disease (Per Investigator)	1	31 (25%)	60 (24%)
	2	35 (28%)	87 (35%)
	3	48 (39%)	83 (34%)
	≥4	9 (7%)	16 (7%)
WHO Performance Score	0	60 (49%)	118 (48%)
	1	63 (51%)	128 (52%)

* Median age and range

The majority of patients enrolled on this study were from the European Union as is summarized in Table 3. The US was the third highest accruing country with 12% of the patients. Overall, the patient accruals to each arm of the study appeared to be well balanced.

Table 3 Summary of enrollment by country on the Phase 3 Trial

Country	Centers	Subjects		
		Placebo (n=123)	Pazopanib (n=246)	Total (n=369)
France	8	22 (18%)	48 (20%)	70 (19%)
Japan	9	16 (13%)	31 (13%)	47 (13%)
USA	7	17 (14%)	26 (11%)	43 (12%)
Korea	6	8 (7%)	26 (11%)	34 (9%)
Italy	7	8 (7%)	22 (9%)	30 (8%)
Germany	8	13 (11%)	14 (6%)	27 (7%)
Belgium	4	8 (7%)	17 (7%)	25 (7%)
Netherlands	4	8 (7%)	17 (7%)	25 (7%)
Australia	5	6 (5%)	16 (7%)	22 (6%)
UK	6	7 (6%)	12 (5%)	19 (5%)
Sweden	5	5 (4%)	12 (5%)	17 (5%)
Spain	2	3 (2%)	3 (1%)	6 (2%)
Denmark	1	2 (2%)	2 (<1%)	4 (1%)

As noted earlier, patients with multiple different diagnoses of STS were eligible for enrollment on the phase 3 study. Patients were enrolled based upon local histopathological review; however pathological specimen from all patients had to be sent to central pathology for secondary review. The results of central pathology review were then used for all efficacy analysis. In cases were central pathology review could not be performed, local results were used. Patients were then classified into 3 different

subgroups of leiomyosarcoma, synovial sarcoma and “other” STS for the efficacy analysis. Based on FDA review, however; the results of central pathology review were not confirmed or were discordant with the local review in 118 (32%) patients. In the majority of these cases of discordance, the disagreement was in regards to STS subtypes that were eligible and classifiable within the same pre-specified STS subgroup with only 5 patients (1%) who were found to have an ineligible histological diagnosis. The results of the patient enrollment based on histological subgroup assignment for the ITT population and for cases whose histological subgroup assignment was centrally confirmed is summarized in Table 4.

Table 4 Patient enrollment on the Phase 3 Trial based on histological subgroup

	ITT Population Analysis		Centrally Confirmed Population	
Histology	**Placebo (n=123)**	**Pazopanib (n=246)**	**Placebo (n=101)**	**Pazopanib (n=201)**
Leiomyosarcoma	49 (40%)	109 (44%)	39 (39%)	96 (48%)
Synovial Sarcoma	13 (11%)	25 (10%)	14 (14%)	24 (12%)
Other	61 (49%)	112 (46%)	48 (47%)	81 (40%)

Based on the results of the central pathology review, a higher proportion of patients on the pazopanib arm had a diagnosis of leiomyosarcoma while the proportion of patients with a diagnosis of “other” STS was higher in the placebo arm. Considering the variable chemo-sensitivity of different histological subtypes of STS, this imbalance can potentially confound the results of the efficacy analysis.

In addition to the discordance reported in the histological diagnosis, significant discordance existed in the tumor grade assignment between the local and central pathology reviews. These results are summarized in Table 5. As can be noted a higher proportion of patients on the placebo arm had high grade disease based on both local and central pathology review. The higher enrollment of patients with high grade disease on the placebo arm may confound the results of this study as these patients have biologically more aggressive disease.

Table 5 Tumor Grade in Patients enrolled on the phase 3 Trial

	Local Pathology		Central Pathology	
Tumor Grade	**Placebo (n=123)**	**Pazopanib (n=246)**	**Placebo (n=123)**	**Pazopanib (n=246)**
High	90 (73%)	159 (64%)	44 (36%)	72 (29%)
Intermediate	30 (25%)	63 (26%)	29 (23%)	70 (29%)
Low	3 (2%)	24 (10%)	11 (9%)	33 (13%)
Unknown/Unclassifiable	0	0	39 (32%)	71 (29%)

Pre-treatment Anti-Cancer Therapy

The number of patients receiving prior local and systemic therapy on the two arms of the phase 3 trial was generally well balanced. This data is summarized in Table 6 and Table 7.

Table 6 Prior Anti-Cancer therapy for patients on the Phase 3 Trial

	Placebo (n=123)	Pazopanib (n=246)	Total (n=369)
Systemic Therapy	123 (100%)	246 (100%)	369 (100%)
Neo-adjuvant	19 (15%)	31 (13%)	50 (14%)
Adjuvant	26 (21%)	43 (17%)	69 (19%)
Advanced, 1 Line	39 (32%)	98 (40%)	137 (37%)
Advanced, 2 Lines	43 (35%)	83 (34%)	126 (34%)
Advanced, 3 Lines	19 (15%)	35 (14%)	54 (15%)
Advanced, 4 Lines	9 (7%)	16 (7%)	25 (7%)
Maintenance	4 (3%)	10 (4%)	14 (4%)
Surgery	114 (93%)	224 (91%)	338 (92%)
Radiation Therapy	75 (61%)	128 (52%)	203 (55%)

Table 7 Prior anti-cancer agents received by patients on the Phase 3 Trial

Type of therapy	Placebo (n=123)	Pazopanib (n=246)	Total (n=369)
Anthracyclines^	121 (98%)	243 (99%)	363 (98%)
Ifosfamide	93 (76%)	164 (67%)	257 (70%)
Docetaxel	35 (28%)	69 (28%)	104 (28%)
Gemcitabine	42 (34%)	85 (35%)	127 (34%)
Trabectedin	22 (18%)	38 (15%)	60 (16%)
Dacarbazine*	19 (15%)	38 (15%)	57 (15%)
Cisplatin*	14 (11%)	28 (11%)	42 (11%)
mTOR inhibitors#	7 (6%)	14 (6%)	21 (6%)

^ Includes doxorubicin, liposomal doxorubic, epirubicin and pirarubicin
* Monotherapy or as part of multi-agent regimen
# This consists of patients receiving unspecified mTOR inhibitor, rapamycin or having been randomized to ridaforolimus vs. placebo.

Post-treatment Anti-Cancer Therapy

In contrast to the balance in pre-study anti-cancer therapies, more patients on the placebo arm received follow-up therapy after withdrawal of study treatment, on the phase 3 trial. This imbalance consisted of an increased number of patients receiving other systemic therapy and or radiation therapy. The distribution of post-treatment anti-cancer therapy and specific agents received is summarized in Table 8 and Table 9.

It is unclear whether this imbalance in post-treatment anti-cancer therapies, can affect the final OS results of this trial, as the magnitude of survival benefit achieved from these therapies, if any at all, is unknown.

Table 8 Distribution of post-treatment anti-cancer therapy on the Phase 3 Trial

	Placebo (N=123)	Pazopanib (N=246)
Any Anti-Cancer Therapy	92 (75%)	149 (61%)
Systemic Therapy	83 (67%)	127 (53%)
Radiotherapy	33 (27%)	49 (20%)
Surgery	9 (7%)	20 (8%)
Other	4 (3%)	7 (3%)

Table 9 Summary of agents used for post-treatment systemic therapy on the Phase 3 Trial

Systemic agent	Placebo (n=123)	Pazopanib (n=246)
Trabectedin	39 (32%)	62 (25%)
Gemcitabine	28 (23%)	42 (17%)
Taxane	23 (19%)	26 (11%)
Ifosfamide/Trofosfamide	21 (17%)	25 (10%)
Dacarbazine/Temozolomide	17 (14%)	25 (10%)
Angiogensis Inhibitor	16 (13%)	21 (9%)
Etoposide	10 (8%)	17 (7%)
Anthracyclines	9 (7%)	15 (6%)
Cyclophosphamide	8 (7%)	14 (6%)
Carboplatin/Cisplatin	9 (7%)	10 (4%)
mTOR	6 (5%)	1 (<1%)
Navelbine	3 (2%)	4 (2%)

Disposition

Table 10 summarizes the treatment status and reasons for discontinuation of study therapy in the ITT Population, as assessed by the investigators and applicant at the time of the finalized OS data submission (data cutoff date of October 24, 2011). At the time of data cut-off, 6 (2%) patients remained on study, all of which are on the pazopanib arm. More patients on the placebo arm discontinued study therapy due to progression (97% on placebo vs. 72% on pazopanib) while the proportion of patients discontinuing study therapy due to toxicity was higher in the pazopanib arm (1% on placebo vs. 14% on pazopanib). Additionally, more patients discontinued/refused further study therapy on the pazopanib arm (6% vs. 1%).

In the 34 patients on the pazopanib arm who discontinued therapy due to drug related toxicity, the most common primary reason reported by the investigators were liver toxicity in 7 patients, a hemorrhagic event in 4 patients and hypertension, proteinuria and myocardial dysfunction in 3 patients each.

An additional 7 patients on the pazopanib arm were reported to have discontinued therapy due to an adverse event that was assessed by the investigator as not related to study therapy. One of these patients had myocardial dysfunction and another one developed irreversible congestive heart failure (CHF) that contributed to eventual death. Based on FDA analysis, it is likely that the patient with CHF had pazopanib related cardiotoxicity. In the other case of myocardial dysfunction, the patients presentation is confounded by the presence of cardiac metastasis treated with external beam radiotherapy. Both patients had previously received anthracyclines.

Table 10 Patient Disposition for the Phase 3 Trial at time of Final OS Analysis

Disposition	Placebo n (%)	Pazopanib n (%)
Randomized	**123 (100)**	**246 (100)**
On study therapy	**0**	**6 (2)**
Discontinued therapy	**123 (100)**	**240 (98)**
Died	95 (77)	185 (75)
Discontinued therapy, in follow up	24 (20)	46 (19)
Withdrew from study	4 (3)	9 (4)
Reason for discontinuation of therapy		
Progression/Death due to progression	119 (97)	178 (72)
Toxicity/death related to study drug	1 (1)	34 (14)
Patient's refusal\decision	1 (1)	14 (6)
Adverse Event not related to study drug	2 (2)	7 (3)
Inter-current death[#]	0	3 (1)
Protocol violation	0	3 (1)
Other	0	1 (<1)

[#] Unrelated to study drug or malignant disease.

5.2 Efficacy

5.2.1 Primary Endpoint

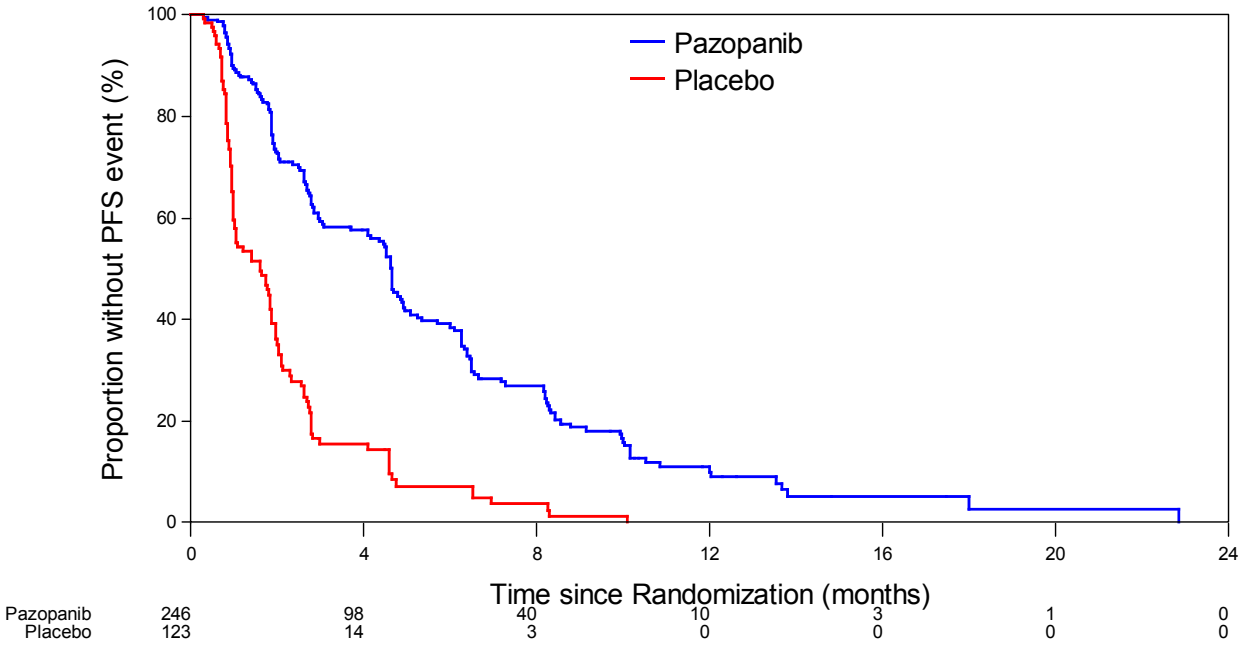
The primary analysis of PFS was based on independent radiology committee review, using a stratified log-rank test in the ITT population. The median PFS was 1.6 months in the placebo arm and 4.6 months in the pazopanib arm, with a corresponding HR of 0.35 (95% CI: 0.26, 0.48) under the adjustment of the two stratification factors, as presented in Table 11. The Kaplan-Meier curves are shown in Figure 2.

Table 11 Progression-free Survival per IRC Review, ITT Population*

	Placebo (n=123)	Pazopanib (n=246)
Patient Classification, n(%)		
Progressed or died	106 (86)	163 (66)
Censored	17 (14)	83 (34)
Kaplan-Meier Estimate for PFS (months)		
Median (95% CI)	4.6 (4.1, 4.9)	1.6 (1.0, 1.9)
Adjusted hazard ratio (95% CI)[a]	0.35 (0.26, 0.48)	
Stratified log rank p-value [a]	<0.001	

* Applicant analysis. Confirmed by FDA.
[a] Hazard ratio is estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log rank test are adjusted for WHO PS and number of prior lines of systemic treatment for advanced disease.

Figure 2 Kaplan-Meier Curves of PFS per IRC, for ITT Population



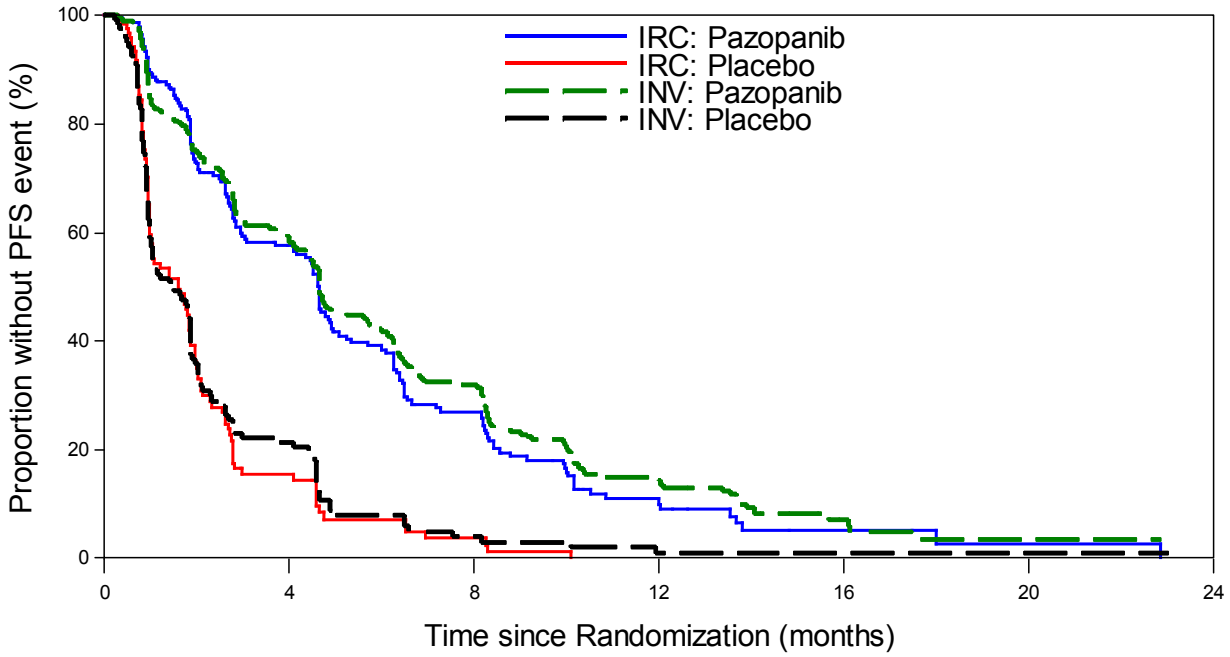
A sensitivity analysis of PFS based on investigator assessments (INV) was conducted to evaluate the consistency of the primary analysis. This analysis included 192 PFS events (78%) in the pazopanib arm and 117 PFS events (95%) in the placebo arm. The estimated medians of PFS in the pazopanib arm and the placebo arm were 4.6 and 1.5 months, respectively, with a HR of 0.39 (95% CI: 0.30, 0.52). PFS results per investigator assessments are presented in the Table 12. Kaplan-Meier curves per INV and IRC demonstrate the consistency of these results and are illustrated in Figure 3.

Table 12 Progression-free Survival based on Investigator Assessment

	Placebo (n=123)	Pazopanib (n=246)
Patient Classification, n(%)		
Progressed or died	117 (95)	192 (78)
Censored	6 (5)	54 (22)
Kaplan-Meier Estimate for PFS (months)		
Median (95% CI)	1.5 (1.0, 1.9)	4.6 (4.3, 5.7)
Adjusted hazard ratio (95% CI)[a]	0.39 (0.30, 0.52)	
Stratified log rank p-value [a]	<0.001	

[a] Hazard ratio is estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log rank test are adjusted for WHO PS and number of prior lines of systemic treatment for advanced disease.

Figure 3 Kaplan-Meier Curves for PFS based on Investigator and IRC



5.2.2 Secondary Endpoints

Overall Survival

The final OS analysis was conducted when 280 death events had occurred (cutoff date: 24 October 2011). In the final analysis, the median OS in the placebo arm was 10.7 months (95% CI: 9.0, 13.1) and in the pazopanib arm was 12.6 months (95% CI: 10.9, 14.9), with a HR of 0.87 (95% CI: 0.67, 1.12), as shown in Table 13. The results did not reach the pre-specified level of significance of P ≤ 0.044 as determined by the Lan and

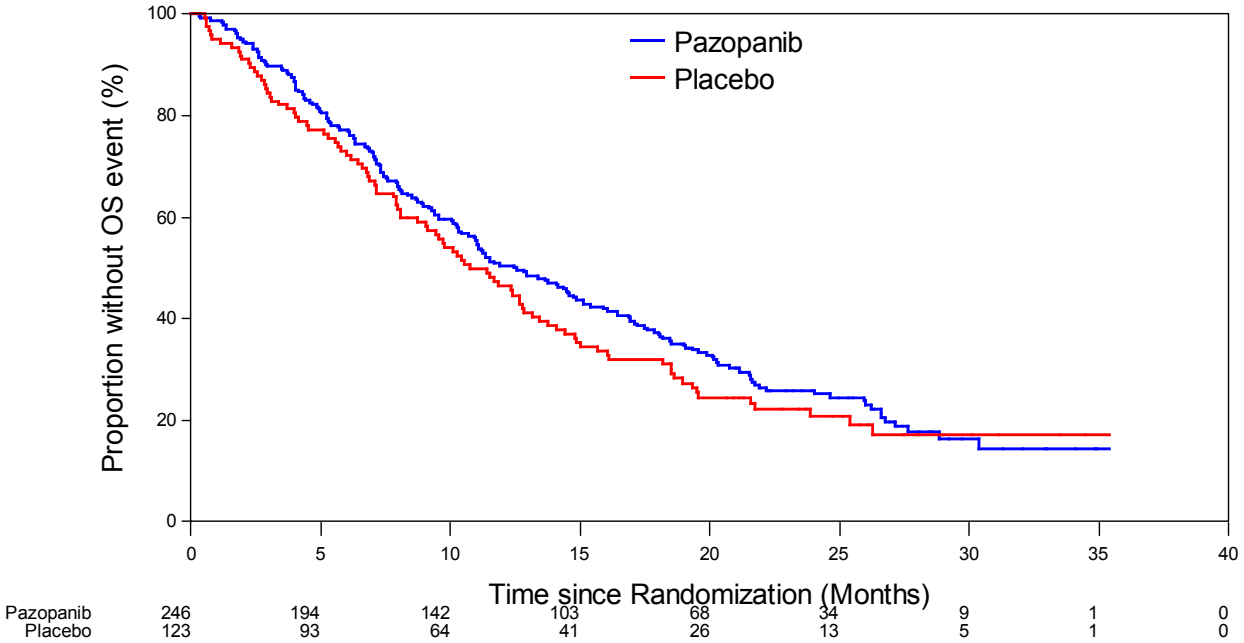
DeMets alpha-spending function with an O'Brien and Fleming boundary. The Kaplan-Meier curves for final OS are shown in Figure 4.

Table 13 Summary of Final Analysis of Overall Survival, ITT Population

	Placebo (n=123)	Pazopanib (n=246)
Died (event), n (%)	95 (77)	185 (75)
Median (95% CI), months	10.7 (9.0, 13.1)	12.6 (10.9, 14.9)
Adjusted hazard ratio (95% CI) [a]	0.87 (0.67, 1.12)	
Stratified log rank p-value [a]	0.26	

[a] Hazard ratio is estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log rank test are adjusted for WHO PS and number of prior lines of systemic treatment for advanced disease.

Figure 4 Kaplan-Meier Curves for Final Overall Survival, ITT Population



Overall Response Rate (ORR)

There were no complete responses in either arm of the phase 3 study. However based on IRC review, 11 patients (4%) on the pazopanib arm had a partial response by RECIST v. 1.0 criterion. The responders included 5 patients with leiomyosarcoma, and 1 patient each with synovial sarcoma, pleomorphic myogenic sarcoma, angiosarcoma, malignant peripheral nerve sheet tumor (MPNST), undifferentiated pleomorphic sarcoma and low grade myxoid sarcoma. This data in addition to results of ORR assessment by investigator are summarized in Table 14.

Table 14 Overall Response Rates on Phase 3 Trial

	IRC Review		Investigator Review	
	Placebo (N=123)	**Pazopanib (N=246)**	**Placebo (N=123)**	**Pazopanib (N=246)**
Best Response	N (%)	N (%)	N (%)	N (%)
CR	0	0	0	0
PR	0	11 (4)	0	23 (9)
SD	33 (27)	134 (54)	36 (29)	138 (56)
PD	76 (62)	66 (27)	83 (67)	70 (28)
Not Evaluable	14 (11)	35 (14)	4 (3)	15 (6)
(CR+PR) 95% CI	0 (0.0, 3.0)	4% (2.3, 7.9)	0 (0.0, 3.0)	9% (6.0, 13.7)

5.2.3 Subgroup Analyses

Subgroup analyses of PFS were performed for each histology subgroup (leiomyosarcoma, synovial sarcoma and 'other' STS) in addition to each tumor grade subgroup (low and intermediate grade vs. high grade). This analysis was performed to ensure consistency of results in an otherwise heterogeneous patient population. These results are summarized in Table 15 and Table 16. In addition, further subgroup analyses were performed by limiting the patient population to patients whose histological diagnosis was centrally confirmed and also by tumor grade based on central review. In each case the HR remained consistent with an improvement in median PFS for the pazopanib arm as compared to placebo.

Table 15 PFS by histological subgroup for ITT population

	Placebo (N=123)	**Pazopanib (N=246)**	**HR (95% CI)***
Leiomyosarcoma			
N	49	109	0.37 (0.23, 0.60)
Number of PFS events (%)	42 (86%)	73 (67%)	
Median in months (95% CI)	1.9 (1.7, 2.1)	4.6 (3.0, 5.3)	
Synovial Sarcoma			
N	13	25	0.43 (0.19, 0.98)
Number of PFS events (%)	13 (100%)	17 (68%)	
Median in months (95% CI)	1.0 (0.7, 2.0)	4.1 (2.0, 6.2)	
'Other' STS			
N	61	112	0.39 (0.25, 0.60)
Number of PFS events (%)	51 (84%)	73 (65%)	
Median in months (95% CI)	1.0 (0.9, 1.8)	4.6 (3.0, 6.1)	

* Hazard ratio is estimated using the Pike estimator adjusted for WHO PS and number of prior lines of systemic treatment for advanced disease. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo.

Table 16 PFS by Tumor Grade as assessed by Local Review (ITT Population)

	Placebo (N=123)	Pazopanib (N=246)	HR (95% CI)*
Low/Intermediate Grade			
N	33	87	0.36 (0.19, 0.67)
Number of PFS events (%)	26 (79%)	51 (59%)	
Median in months (95% CI)	2.1 (1.8, 2.8)	6.2 (4.5, 8.2)	
High Grade			
N	90	159	0.35 (0.25, 0.50)
Number of PFS events (%)	80 (89%)	112 (70%)	
Median in months (95% CI)	1.0 (0.9, 1.7)	4.4 (2.8, 4.6)	

* Hazard ratio is estimated using the Pike estimator adjusted for WHO PS and number of prior lines of systemic treatment for advanced disease. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo.

5.2.4 Other Studies

VEG20002

VEG20002 was a pilot Phase 2 study assessing the activity of pazopanib dosed at 800 mg daily in patients with high or intermediate grade STS incurable by surgery or radiotherapy. The primary objective of this study was to assess progression-free (PF) rate at 12 weeks (number of patients with CR+PR+SD) after start of treatment in the ITT population in addition to 4 histological subgroups of leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and "other" sarcoma subtype. The study enrolled 142 subjects with predominantly intermediate or high-grade STS; 140 of them had received either one or two prior cytotoxic therapies in the neo-adjuvant and/or advanced disease setting. Efficacy results were based on the 138 subjects in the ITT Population. These results are summarized in Table 17. The adipocytic sarcoma subgroup was closed early due to lack of activity although subsequent central pathology re-classification of tumors suggests evidence of early activity in this subgroup.

Table 17 Progression-free Rate at 12 weeks on the Phase 2 Study

Category	Leiomyo. N=41	Adipocytic N=19	Synovial N= 37	Other STS N=41	Total N=138
CR+PR+SD, n (%)	17 (41)	5 (26)	18 (49)	17 (41)	57 (41)
90% CI	(28.4, 55.5)	(11.0, 47.6)	(34.3, 63.2)	(28.4, 55.5)	(34.2, 48.7)
p-value*	0.003	0.653	<0.001	0.003	<0.001

* P-value is for a test against null hypothesis of progression-free rate ≤ 0.20

5.3 Safety

5.3.1 Safety Population

Based on the 2011 Investigators Brochure for pazopanib, over 5300 patients with cancer have been exposed to pazopanib on clinical trials as of September 9, 2010. This includes 240 patients with STS who received at least one dose of study therapy on the pazopanib arm of the randomized phase 3 study and 142 treated on the phase 2 open label study. The dose of pazopanib used in the STS studies, was 800 mg, PO, QD which is the same as the currently approved dose for RCC. Complete adverse event information for the 240 patients who received pazopanib in the Phase 3 study will be examined along with examination of supportive data from the phase 2 study.

5.3.2 Exposure

Table 18 below provides information on the number of patients who required dose reductions or delays as well as the median duration of exposure to pazopanib or placebo on the Phase 3 trial. One hundred and forty patients (58%) had a dose interruption on the pivotal study while 94 (39%) had a dose reduction. An additional 34 patients (14%) on the pazopanib arm had their study therapy discontinued due to toxicity. These patients were discussed in section 5.1 Patient Populationand summarized in Table 10.

Table 18 Exposure to study treatment on the Phase 3 Trial

	Placebo (N=123)	**Pazopanib (N=240)**
Median Time on Treatment (Weeks) (Range)	8.1 (1.1, 131.9)	19.4 (0.3, 146.3)
Median Daily Dose (mg) (Range)	800.0 (432.1-800.0)	793.1 (249.4, 800.0)
Dose Interruptions	15 (12%)	140 (58%)
≥ 2 Dose Interruptions	2 (2%)	72 (30%)
Dose Reductions	5 (4%)	94 (39%)
≥ 2 Dose Reductions	1 (1%)	39 (16%)

The four adverse events most commonly contributing to a dose reduction and/or a dose interruption were fatigue, diarrhea, hypertension and nausea. Other important AEs leading to dose modifications included skin disorder (hand and foot syndrome) and exfoliative rash, elevated liver transaminases and left ventricular dysfunction.

5.3.3 Deaths

Table 19 summarizes the status of patients on the phase 3 study at the time of the final OS analysis (October 24, 2011). Most patient deaths were attributed to progressive disease although the deaths of two patients on the pazopanib arm were attributed to "Non-Hematologic Toxicity". One of these patients died after developing hepatic failure on pazopanib therapy while the second patient died of renal failure while receiving follow up chemotherapy after progression and withdrawal of pazopanib.

The death of a third patient on pazopanib was attributed to "Cardiovascular disease not due to toxicity" by the applicant; however based on FDA review this patient developed congestive heart failure while receiving pazopanib therapy which led to withdrawal of therapy and discharge to hospice. This patient died of cardiorespiratory arrest on day 25 after the last dose of pazopanib. In addition, two of the patients whose deaths were attributed to unrelated adverse events died of aspiration pneumonia and pneumonia due to an ambulant drain placed secondary to pneumothorax. The contribution of pazopanib therapy to these deaths can not be ruled out.

Table 19 Summary of Deaths on Phase 3 Trial

Patient Status	Placebo (N=123)	Pazopanib (N=240)
Death	95 (77)	181 (75)
Death not reported	28 (23)	59 (25)
Primary Cause		
Progression of Disease	86 (70%)	165 (69%)
Non-hematologic Toxicity	1 (<1%)	2 (<1%)
Cardiovascular disease	0	1 (<1%)
New primary cancer	1 (<1%)	0
Unrelated Adverse Event	2 (2%)	3 (1%)
Other	1 (<1%)	3 (1%)
Unknown	4 (3%)	7 (3%)

On the phase 2 study VEG20002, 3 patients died following a therapy related AE. The causes of death in these patients included peritonitis secondary to GI perforation, death following sever mood alteration and anorexia and disseminated intravascular coagulation.

5.3.4 Adverse Events

The proportion of patients experiencing any non-fatal adverse reaction, a grade 3-4 AE or an SAE was significantly higher on the pazopanib arm of the randomized phase 3 trial when compared to the placebo. These results are summarized in Table 20.

In addition, 47 (20%) patients on the pazopanib arm experienced an AE that led to discontinuation of therapy. In some of these cases the AE was due to or was coincident with disease progression, hence discontinuation of therapy was attributed to pazopanib in only 34 of these patients (Table 10). The AEs most commonly contributing to discontinuation of therapy included ALT elevation, left ventricular dysfunction, dyspnea, pulmonary embolism, fatigue, hypertension and vomiting.

Table 20 Summary of Adverse Events on Phase 3 Trial

	Placebo (N=123)	**Pazopanib (N=240)**
Grade 1-4 AEs*	110 (89%)	237 (99%)
Grade 3-4 AEs*	32 (26%)	150 (63%)
SAE	29 (24%)	98 (41%)
AE leading to discontinuation	6 (5%)	47 (20%)

* AEs graded based on CTCAE v. 3.0 Criteria.

Based on FDA review, the overall AE profile in patients with STS was generally consistent with the currently known AE profile in RCC with some differences. The AE profile of pazopanib in the RCC patient population included fatal hepatotoxicity, fatal hemorrhagic events, fatal gastrointestinal (GI) perforations, torsades de pointes and hypertensive crisis. Similarly in the STS population reported AEs included fatal hepatotoxicity, fatal GI perforation, life threatening hemorrhagic events and severe hypertension (systolic BP> 170 mmHg). Additional AEs noted with increased frequency in the STS population included myocardial dysfunction, thromboembolism and pneumothorax. The AEs of hepatotoxicity, myocardial toxicity, hypertension, hemorrhagic events, thromboembolic events, pneumothorax and hypothyroidism are considered to be AEs of clinical relevance in the STS patient population and are individually discussed below.

Hepatotoxicity

The current labeling for pazopanib contains a box warning regarding episodes of fatal hepatotoxicity observed in clinical trials with pazopanib. Based on the FDA review of data from the phase 3 STS study, 11% of patients on the pazopanib arm had a grade 3 rise in ALT or AST levels as compared to 4% on the placebo arm. Most cases improved with dose modifications; however 3 patients on the pazopanib arm had clinical evidence of liver failure at the time of death. Although all cases are confounded, the role of pazopanib in development of hepatic failure in at least one case is probable.

Myocardial Dysfunction

Baseline and follow up measurements of LVEF were available for a subset of 142 patients (59%) on the pazopanib arm and 40 patients (33%) on the placebo arm of the

phase 3 trial. Although incomplete, the data from this study suggest an increased incidence of myocardial dysfunction in the patients receiving pazopanib. Myocardial dysfunction for the purposes of this study was defined through an examination of changes from baseline in LVEF using the following criteria:

- symptoms of myocardial dysfunction or,
- ≥15% absolute decline in LVEF compared to baseline or,
- ≥10% absolute decline in LVEF compared to baseline that is also below the lower limit of normal (LLN).

This data is summarized in Table 21.

Table 21 Summary of cases of LVEF decline and Myocardial Dysfunction on the Phase 3 Trial

# of Patients	Placebo (n=123)	Pazopanib (n=240)
Baseline and follow up LVEF	40 (33%)	142 (59%)
Any LVEF Decline	17 (14%)	89 (37%)
Myocardial Dysfunction	2 (2%)	16 (7%)
Symptomatic CHF	0	3 (1%)*

* One patient had irreversible CHF that led to study withdrawal and contributed to death from "cardio respiratory arrest".

Hypertension

Hypertension is an AE commonly seen in association with anti-VEGF agents including pazopanib. In the phase 3 study, 40% of the patients on the pazopanib arm had an increase in systolic blood pressure to levels ≥150 while on study. Twenty nine (12%) of these patients had an increase in systolic BP to ≥170 mmHg. Similarly, 56% of the patients on the pazopanib arm had a diastolic BP of ≥90 mmHG. These rates are similar to the hypertension rates observed in RCC patients although there were no AEs of hypertensive crisis reported in the phase 3 STS study.

Hemorrhagic events

In the phase 3 study, the overall incidence of hemorrhagic events (any grade) was higher in the pazopanib arm (22%) compared to the placebo arm (8%). This included 6 grade 3-4 events (3%) on the pazopanib arm as opposed to 2 (2%) on the placebo arm. The three grade 4 hemorrhagic AEs on the pazopanib arm were intracranial hemorrhage, subarachnoid hemorrhage and peritoneal hemorrhage.

Thromboembolic Events

Thirteen patients (5%) on the pazopanib arm and 3 patients (2%) on the placebo arm of the phase 3 trial experienced venous thromboembolism. Ten (4%) patients on pazopanib developed deep venous thrombosis (DVT) while 3 (1%) patients experienced

pulmonary embolism (PE). PE was a fatal AE in 2 of these patients. In addition to the patients with venous thromboembolic events, 5 patients (2%), all on pazopanib arm, experienced an event of arterial thromboembolism (4 patients had a myocardial infarction and one patient an episode of cerebral infarction that occurred after study withdrawal). As the event of cerebral infarction occurred after pazopanib withdrawal, the contribution of pazopanib to the AE is unlikely. This data is summarized in Table 22.

Table 22 Incidence of Thromboembolic AEs on Phase 3 Study

	Placebo (N=123)	**Pazopanib (N=240)**
Venous Thromboembolism	**3 (2)**	**13 (5)**
DVT	2 (2)	10 (4)
PE	1	3 (1)[a]
Arterial Thromboembolism	**0**	**4 (2)**
MI	0	4

[a] includes 2 fatal PE

Pneumothorax

In the phase 3 study, 8 patients (3%) in the pazopanib arm, compared to none on the placebo arm, experienced an episode of pneumothorax. In one patient this led to withdrawal of therapy and another patient required placement of an ambulant drain and subsequently developed pneumonia and died. On the phase 2 study, VEG20002, an additional 7 patients (5%) had a pneumothorax. Although all of the patients in the phase 3 study had pulmonary metastases, 3 patients in the phase 2 study did not have evidence of pulmonary metastasis.

Hypothyroidism

Patients on VEG110727 had routine monitoring at baseline and every 12 weeks. Twenty patients (8%) on the pazopanib arm of the phase 3 study were reported by the investigators to have an AE of hypothyroidism. No patients on the placebo arm were reported to have hypothyroidism.

6. Conclusion

STS are a rare, heterogeneous family of tumors of mesenchymal origin. Patients with metastatic STS have a median survival of approximately one year and judicious use of chemotherapy can generally reduce disease burden, delay progression and improve quality of life. However, even though many experts believe the use of chemotherapy may provide a survival benefit, because of the clinical heterogeneity of this disease and the variable response to chemotherapeutic agents, there is a paucity of well controlled clinical data demonstrating this benefit.

Pazopanib is an anti-VEGF agent currently marketed for the treatment of advanced RCC. The applicant performed a randomized phase 3 study demonstrating a statistically significant improvement in PFS with a difference in median PFS of 3 months in patients with metastatic STS treated with pazopanib when compared to patients receiving placebo (HR=0.35). This PFS benefit is consistent in all STS histology subgroups studied but it does not translate into a statistically significant overall survival benefit. There is no clear explanation for the inconsistency between the PFS and OS benefits although there appears to be an imbalance in the number of patients who received follow up anti-cancer therapy. An alternative explanation would be that a larger PFS effect would be necessary to achieve a parallel OS benefit.

The safety profile of pazopanib in patients with STS is generally similar to the safety profile in patients with RCC, which includes severe adverse reactions that led to therapy discontinuation or death. Additional adverse reactions noted with higher frequency in the STS population include myocardial dysfunction, thromboembolism and pneumothorax.

Draft question for ODAC: Considering the observed improvement in PFS, the absence of an improvement in OS, and the adverse event profile of pazopanib, is the risk benefit assessment favorable for the use of pazopanib in the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy.